6-[^{18}F]Fluorodopamine
6-[^{18}F]FDA

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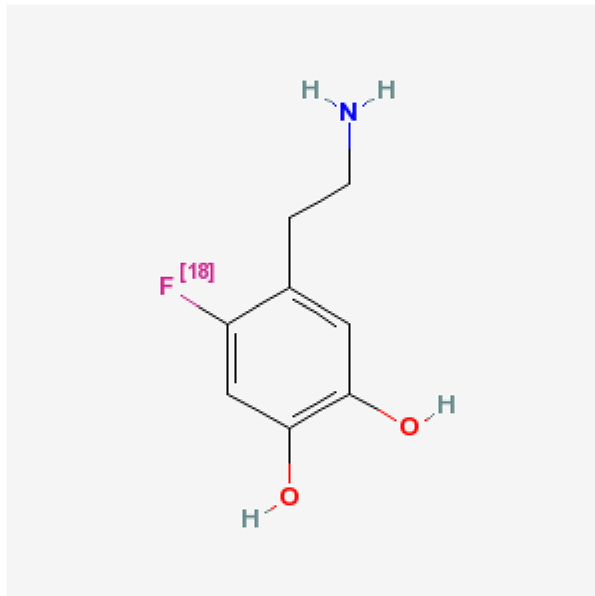
Chemical name:	6-[^{18}F]Fluorodopamine
Abbreviated name:	6-[^{18}F]FDA, [^{18}F]FDA
Synonym:	
Backbone:	Compound
Target:	Sympathetic neuron transporters and dopamine β-hydroxylase
Mechanism:	Uptake, conversion to norepinephrine and vesicle storage
Method of detection:	PET
Source of signal:	^{18}F
Activation:	No
***In vitro* studies:**	Yes
Rodent studies:	Yes
Other non-primate mammal studies:	Yes
Non-human primate studies:	Yes
Human studies:	Yes



Click on the above structure for additional information in PubChem [http://pubchem.ncbi.nlm.nih.gov/].

Background

[PubMed]

Dopamine, a neurotransmitter, plays an important role in the mediation of movement, cognition, and emotion. Parkinson's disease (PD) is associated with a loss of dopamine-containing neurons in the striatum of the brain (1, 2). Dopamine is synthesized within nerve cells (3). Chemically, L-tyrosine is converted to dihydroxyphenylalanine (L-DOPA) and then to dopamine in a two-step process. The first rate-limiting step is catalyzed by tyrosine 3-monoxygenase (tyrosine hydroxylase or TH). The second step is catalyzed by aromatic L-amino acid decarboxylase (L-DOPA decarboxylase, AAAD). In dopaminergic neurons, dopamine is not metabolized further and is stored in vesicles in the presynaptic nerve terminals. Interstitial dopamine is recaptured by the dopamine transporter, DAT.

In noradrenergic neurons, dopamine is converted to norepinephrine (NE) by dopamine β-hydroxylase and stored in vesicles in the neurons (4). Released NE in synaptic junctions is either inactivated by COMT in postsynaptic cells or transported by a NE transporter (NET) into the nerve terminals (uptake-1). Dopamine is also efficiently transported by NET. At extraneuronal locations, DAT is present in the placenta and lung endothelial cells, and NET is present in the stomach and pancreas. There are also three non-neuronal transporters functioning in peripheral tissues such as the heart, liver, kidneys, intestine, blood vessels, retina, and placenta. These uptakes by non-neuronal cells are termed uptake-2.

After transported into sympathetic nerve endings by uptake-1, 6-[^{18}F]FDA is rapidly converted to 6-[^{18}F]fluoronorepinephrine (6-FNE) by dopamine β-hydroxylase in neuronal vesicles (5). 6-[^{18}F]FDA is also metabolized via mitochondrial monoamine oxidase to yield [^{18}F]6-fluoro-3,4-dihydroxyphenylacetic acid (FDOPAC). In nonneuronal cells, 6-[^{18}F]FDA is converted by COMT sequentially to *O*-[^{18}F]methoxytyramine and [^{18}F]6-fluorochomovanillic acid (FHVA). FDOPAC taken up after release from sympathetic neurons by uptake-2 is converted to FHVA by COMT. Uptake of 6-[^{18}F]FDA into sympathetic nerve terminals, with conversion to and storage of 6-[^{18}F]FNE in vesicles, would lead to more intense positron emission tomography (PET) signals from sympathetically innervated tissues than non-innervated tissues.

Synthesis

[PubMed]

6-[^{18}F]FDA was synthesized from 6-[^{18}F]FDOPA by enzymatic decarboxylation using AAAD prepared from hog kidneys with a radiochemical purity of >98% and a specific activity of 37 MBq/mg (1 mCi/mg) (5). A direct synthesis was also used to produce a higher specific activity. *N*-(Trifluoroacetyl)-3,4-dimethoxy-6-trifluoroacetoxymercuro-β-phenethyamine was fluorodemercurated by [^{18}F]F_2 to form 6-[^{18}F]FDA with a radiochemical purity of 98% and about 22 MBq/mmol (800 mCi/mmol) at the end of synthesis (6).

To obtain a higher specific activity, a multi-step synthesis of 6-[^{18}F]FDA using nucleophilic aromatic substitution by [^{18}F]fluoride ion/Kryptofix2.2.2 was achieved in 105 min with a radiochemical yield of 20% and a specific activity of 74-185 GBq/μmol (2-5 Ci/μmol) at the end of bombardment (7). Chemical and radiochemical purities were >98%.

6-[^{18}F]FDA was routinely synthesized by the direct fluorination of dopamine with [^{18}F]KF using the standard [^{18}F] potassium Kryptofix complex (8). Reverse-phase high-performance liquid chromatography was used to separate 6-[^{18}F]FDA from the reaction mixture containing 2- and 5-[^{18}F]FDA. The radiochemical yield of 6-[^{18}F]FDA was 10 ± 2% at the end of the 120-min synthesis from the end of bombardment. The specific activity of 6-[^{18}F]FDA was 370 GBq/mmol (10 Ci/mmol) at the end of synthesis.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The enzyme kinetic parameters using Lineweaver-Burk plots for uptake of [^{3}H]DA and 6-[^{18}F]FDA were determined *in vitro* from bovine chromaffin granule membranes (9). The K_m and V_{max} for [^{3}H]DA were 14.7 μM and 1.6 nmol/mg protein-min, respectively. The K_m and V_{max} for 6-[^{18}F]FDA were 15.3 μM and 2.4 nmol/mg protein-min, respectively. FDA showed an affinity comparable to DA. Both uptakes were inhibited by reserpine, an uptake-1 blocker. Unlabeled FDA inhibited uptake of [^{3}H]DA with a K_i of 20.8 μM.

Animal Studies

Rodents

[PubMed]

A high uptake of radioactivity was found in the kidneys, left ventricular myocardium, spleen, salivary gland, and liver of rats at 5 min after injection of [^{3}H]6-FDA (10). The amount of radioactivity was decreased to <3% in plasma in 5 min. Tissue/blood ratios increased progressively from 5 to 120 min. In the heart, the majority of the tissue radioactivity was [^{3}H]6-FDA (17%) and [^{3}H]6-FNE (70%). In the kidneys and liver, [^{3}H]FDA and [^{3}H]FNE contributions were <30%. No [^{3}H]6-FNE was detected in the plasma.

The neuronal uptake and metabolism of 6-[^{18}F]FDA and [^{3}H]dopamine were studied in the heart, submaxillary gland, and spleen. Less 6-[^{18}F]FNE accumulation in tissues than [^{3}H]NE was observed as a result of inefficient hydroxylation of fluorinated dopamine (11). 6-[^{18}F]FDA was rapidly stored in vesicles of sympathetic neurons but was a poorer substrate than [^{3}H]DA to form NE. Accumulation of [^{3}H]catechols in the heart was decreased by 64-88% when unlabeled 6-FDA (250 μg/kg) was co-injected with a trace amount of [^{3}H]DA. Desipramine and reserpine (uptake-1 blockers) pretreatment of rats blocked the tissue accumulation of tritiated and fluorinated dopamine and their dihydroxy-metabolites.

Other Non-Primate Mammals

[PubMed]

In dogs, 6-[^{18}F]FDA PET images were intense in the renal pelvis, heart, liver, kidneys, spleen, and salivary glands, with little signal from the brain, lungs, and skeletal muscle at 1 h after injection (10). Concentrations of radioactivity in blood and plasma fell rapidly with a biologic half-life of 1.5 min. The left ventricular myocardium was strikingly delineated. High radioactivity in the gallbladder and urinary system pointed to the hepatic and renal excretion of the tracer and its metabolites. Treatment with 6-hydroxydopamine (6-OHDA, neurotoxin) or reserpine (uptake-1 blocker) diminished almost completely the signal from the left ventricular myocardium (12). Plasma FDOPAC levels were lowered in 6-OHDA treated dogs and elevated in reserpinized dogs. Decreased PET signal from denervated salivary gland also confirmed that 6-[^{18}F]FDA was accumulated normally in sympathetic neurons (5).

Non-Human Primates

[PubMed]

Comparative PET studies of (-)- and (+)-6-[18F]FNE and of 6-[^{18}F]FDA in the heart were performed in the same baboon (13). There was a longer retention of radioactivity after injection of (-)FNE than for the (+)FNE. There was an initially higher and faster uptake in the heart for 6-[^{18}F]FDA than for FNE. All three tracers disappeared rapidly in plasma. There was a greater washout also for 6-[^{18}F]FDA than for FNE. There was only 1-2% intact FDA as compared with 28% for (-)FNE and 17% for (+)FNE at 10 min after injections. Most of the metabolites were methylated non-catechols. Metabolites appeared more rapidly for FDA than (-)FNE and (+)FNE. Desipramine (a specific NET blocker; 0.5 mg/kg) blocked almost completely the uptake of (-)FNE, and there was a 60-70% recovery of FNE uptake at 24 h after desipramine pretreatment. The uptake of 6-[^{18}F]FDA was only partially blocked by desipramine at the same dosage, suggesting additional reuptake mechanisms for 6-[^{18}F]FDA accumulation in the heart.

Human Studies

[PubMed]

Human dosimetry was estimated in 10 healthy volunteers (14). The bladder wall receives the highest dose (0.22 mGy/MBq or 0.83 rad/mCi). Other organs receiving high doses are the kidneys (0.19 mGy/MBq or 0.71 rad/mCi) and spleen (0.037 mGy/MBq or 0.14 rad/mCi). The liver and lungs receive <0.016 mGy/MBq (0.06 rad/mCi). The effective dose equivalent of 0.0068 mSv/MBq (25 mrem/mCi) was estimated in the intravenous administration of 6-[^{18}F]FDA.

6-[^{18}F]FDA PET scans were obtained in healthy volunteers after intravenous injection of 37-148 MBq (1-4 mCi) 6-[^{18}F]FDA (15). The left ventricular myocardium was visualized in all subjects. Arterial plasma FDA concentration decreased rapidly with a biologic half-life of 2.4 min. FHVA and FDA sulfate appeared rapidly in the plasma. No FNE and its metabolites were detected. Greater than 94% of FDA was excreted mostly as metabolites in urine at 24 h after injection. Desipramine (uptake-1 blocker) decreased the uptake of myocardial radioactivity and plasma FDOPAC. Trimethaphan (TRI), a postganglion nerve traffic blocker, induced higher levels of 6-[^{18}F]FDA PET myocardial signal than untreated subjects. TRI increased FDOPAC plasma levels but decreased FNE levels as compared with untreated subjects. Tyramine (TYR) displaces amines from vesicles and induces release of NE into the synaptic cleft. TYR decreased the 6-[^{18}F]FDA PET myocardial signal more rapidly than in untreated subjects. TYR increased plasma levels of FNE and its metabolite by 30% and 78%, respectively. FDA PET scanning is a useful tool to assess sympathetic innervation and function noninvasively in human myocardium.

6-[^{18}F]FDA PET permits objective monitoring of cardiac sympathetic innervation and function in various disease conditions, such as Parkinson's disease (16), hypertension, and congestive heart failure (17). In recent studies, 6-[^{18}F]FDA has also demonstrated its usefulness in the imaging of chromaffin tumors, neuroblastomas, ganglioneuromas, and metastatic pheochromocytomas (18, 19).

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